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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,972	SCHWAB ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114-119,123-132 and 135-141* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-119,123-132 and 135-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/4/06,11/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks, amendments, and declaration filed 4 October 2006 have been entered. Claims 120 – 122, 133 – 134, are canceled. Claims 138 – 141 are new. Claims 114 – 119, 123 – 132, 135 – 141 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections and Objections

3. The following rejections and objections set forth in the previous office action are withdrawn:

A. The objection to claim 133 as being an improper multiple dependent claim is moot as the claim is canceled.

B. The rejection under 35 USC 112, second paragraph is withdrawn as applicant has amended the claims such that they recite generic chemical names rather than trademarks.

C. The rejections under 35 USC 102 and 103 over Michalovich, Eisenbach-Schwartz, GenBank AF132047, GenBank AB015639 are withdrawn. The amendments to the rejected claims are sufficient to overcome the rejections. The claims no longer recite new matter, so they are entitled to a priority date which antedates each of the references.

D. The rejections under 35 USC 102(b) over Caroni (1988b Journal of Cell Biology 106:1281-1288), Caroni (1988a Neuron 1:85-96), and Spillman (March 1997. European Journal of Neuroscience 9:549-555), are withdrawn in light of the declaration. The declaration by Dr. Schwab, filed provides evidence that in each paper, the proteins were contaminated by central nervous system myelin and therefore is not "free of all central nervous system myelin" as recited in the claims. See declaration, paragraphs (8), (13), and (17) – (18) for example.

E. The rejection of claims 126, 128 – 132 under 35 USC §§ 102(b) over Chen (1997. Society for Neuroscience Abstracts 23:1723. Abstract presented at 27th Annual Meeting of the Society for Neuroscience, 25 – 30 October 1997) are withdrawn in light of the declaration. The declaration by Dr. Schwab states, at paragraph 21, that the clones disclosed to the public at the 1997 Neuroscience meeting "were later shown to represent partial sequences of the Nogo gene". The declaration by Dr. Schwab states, at paragraph (22), that no sequences were disclosed in the declaration, thus the rejection of claims 126 and 128 – 132, drawn to full-length Nogo nucleic acids, are withdrawn.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 112

4. Claims 115 – 116, 118 – 119, 123 – 125, 136, 138 – 141 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for full-length proteins and fusions proteins which inhibit spreading of NIH3T3 fibroblasts or PC12 cells (i.e. SEQ ID NO:2, SEQ ID NO:29, residues 1 – 171 of SEQ ID NO:2 fused to residues 975 – 1163 of SEQ ID NO:2, residues 1-172 of SEQ ID NO:29 fused to residues 990-1178 of SEQ ID NO:29) and proteins which have been shown in the specification to elicit antibodies which attenuate the inhibitory effects of Nogo (i.e. residues 623-640 of SEQ ID NO:2 and residues 762-1163 of SEQ ID NO:2), does not reasonably provide enablement for those fragments claimed that do not inhibit fibroblast spreading, or for fragments which merely are able to elicit antibodies for which no in vitro or in vivo data have been provided, or for fragments which merely bind to certain antibodies, or nucleic acids which encode same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons of record and explained in further detail below. Briefly, the specification discloses at least four proteins which are useful. These are SEQ ID NO:2, SEQ ID NO:29, residues 1 – 171 of SEQ ID NO:2 fused to residues 975 – 1163 of SEQ ID NO:2, and residues 1-172 of SEQ ID NO:29 fused to residues 990-1178 of SEQ ID NO:29. These proteins are useful because they have been demonstrated to inhibit spreading of NIH3T3 fibroblasts or PC12 cells in vitro. As this inhibitory activity prevents regrowth of injured spinal cord neurons and functional recovery after lesion, and antibodies which bind to Nogo-A allow regrowth of injured neurons, it is reasonable that those proteins which actually inhibit spreading could be used to make therapeutic antibodies. Note that SEQ ID NO:2 is rat Nogo A, see specification p. 12 lines 13 – 18, SEQ ID NO:29 is human Nogo A. Because the inhibitory property of the molecule is clearly what is desirable for axon guidance, where such inhibition guides the axon and keeps it on target, and is what is to be blocked when nerve regeneration is desired, this inhibitory function must be present for the claimed invention to be useful. Those embodiments which are not inhibitory (i.e. they don't prevent spreading in a fibroblast or PC12 assay) would not be expected to be useful in any therapeutic setting and thus are inoperative. In the previous office action, the examiner clearly set forth this point. The examiner also indicated that certain fragments of proteins are shown not to be useful in the specification. See

office action mailed 6 April 2006, p. 4 first paragraph and last complete paragraph. The examiner indicated that residues 975 – 1163 of SEQ ID NO:2 are not useful in this context. While this fragment has been canceled in some claims, for example claim 114 and claim 135 (part xviii as numbered previously), applicant has chosen to continue to claim this fragment, for example in new claim 140, part (iii). The specification does not show how to use this fragment. Applicant notes that this fragment, as well as residues 990-1178 of SEQ ID NO:29, the carboxy-terminal 188 amino acids of SEQ ID NO:29, and SEQ ID NO:32 are essentially functionally equivalent and are collectively referred to as Nogo-C (remarks filed 4 October 2006, p. 18, footnote 14).

Briefly, the examiner believes the issue with respect to the fragments which do not induce spreading is as follows. Applicant argues, quite extensively, that the proteins are useful even if they do not induce spreading because they can be used to generate antibodies, and said antibodies can be used to purify those forms of Nogo which are themselves useful. The examiner has set forth that only those proteins which themselves have an activity reasonably correlated with the known activity of Nogo (i.e. inhibiting spreading of 3T3 or PC12 cells) are enabled. Applicant cites MPEP § 2164.01(c), which states in part that "if any use is enabled... the application is enabling for the claimed invention." While this is of course true, applicant is directed to the more relevant section of MPEP, which particularly deals with the question of whether or not enablement is commensurate in scope with the claims. See for example MPEP § 2164.08, which states:

> All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled.... The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). [emphasis added]

Here, the inactive proteins, such as those referred to as Nogo-C and those which have not been shown to inhibit spreading, are claimed. However, the specification does not teach the use of these proteins. Applicant argues that since they can be used to generate antibodies which can later be used to purify useful proteins, the fragments such as Nogo-C are enabled.

As set forth previously, the claimed protein fragments do not share a common core structure which provides for a common utility. The art of record (Hopp et al., 1981) indicates that proteins as small as six amino acids can be used to make antibodies. Clearly since the proteins disclosed are very large by comparison (some are at least 1100 amino acids long), a huge number of possible protein sequences share this characteristic or property, even though they would lack any common sequence. Additionally, the antibodies made by administering inactive fragments such as Nogo-C would most likely bind to the inactive fragments themselves, rather than to the full-length Nogo protein (i.e. that of SEQ ID NO:2 or 29). So if fragments are present in a heterogeneous sample, the antibodies raised against the inactive fragments would be expected to purify those same inactive fragments. If fragments are not present in the heterogeneous sample, the antibodies would be expected to bind to any and all other proteins which contain the same epitope. Since the art teaches that as few as six amino acids can raise an antibody (see Hopp, of record), the antibodies raised against the useless fragments would be expected to have considerable cross-reactivity with other proteins, abrogating any possible use in purifying full-length Nogo. Thus applicant's arguments that fragments which do not inhibit 3T3 or PC12 spreading are in fact useful are not persuasive. This applies not only to claim 140 which recites Nogo-C, but also to all fragments which do not have the ability to inhibit spreading. The specification does disclose specific fragments which in fact have this property; see Figure 18, legend for Figure 18 on pp. 9 – 10 which discloses the sequences corresponding to the block diagrams in the figure, and Table 2 on p. 68 which discloses which fragments actually inhibit spreading. These protein fragments are considered enabled, as are proteins comprising these fragments, as are proteins at least 95% identical to these fragments that inhibit spreading of PC12 or NIH3T3 cells. Similarly, nucleic acids encoding these are also enabled, given the guidance in the specification and the state of the art. However, it would take undue experimentation for the skilled artisan to make and use the rest of the proteins and nucleic acids these proteins.

The claims have been amended to recite particular activities that the claimed proteins or the proteins encoded by the claimed nucleic acids must have. See for example claims 115 and 116, each of which recite seven activities, and claim 138, which requires that the encoded protein have the ability to bind antibodies. With respect to the activities, the only ones that are reasonably enabled are the ability to prevent regeneration of neurons in the spinal cord or brain, the ability to confer to a substrate the property of restricting growth, spreading and migration of

neural cells, ability to inhibit dorsal root ganglia neurite outgrowth, ability to block NIH 3T3 cell spreading, and ability to block PC12 neurite outgrowth. Note claims 114 and 115 each encompass proteins which do not have to have any of these activities, but only need to bind to certain antibodies or be able to generate antibodies which cross-react with other proteins. Claim 138 does not require that the protein encoded by the claimed nucleic acid have any particular activity, only that it bind to certain antibodies. As set forth in considerable detail above, the ability to bind to or elicit an antibody is not considered an enabling claim limitation, as the specification does not teach the public how to use those proteins which bind to antibodies or elicit antibodies. Given that the prior art teaches that only six amino acids need be present for a protein to be antigenic, the specification does not teach the public how to use a reasonable number of members of the very broad genera and sub-genera encompassed by the claims.

Additional claims (for example, claims 135 and 136) do not require that the fragments and variants of certain disclosed protein sequences have any activity. Random protein mutations would be expected to result in inactive proteins. See for example Geysen et al. (1988. Journal of Molecular Recognition 1:32-41), who teach that changing amino acid sequences alters the ability of a protein to be recognized by an antibody, and changes the ability of a protein to elicit an antibody upon administration to an animal.

The specification does not teach the artisan how to use the inactive proteins. Therefore these claims (i.e. 135 and 136) are not enabled over their full scope, as they encompass an unreasonably large number of proteins which would be expected to be inactive. However, applicant does persuasively argue that the proteins of residues 623-640 and 762-1163 of SEQ ID NO:2 would be expected to be useful, as these sequences or very similar ones were shown in the specification to generate antibodies that neutralize the inhibitory activity of Nogo-A (see remarks, p. 23 and specification pages referred to therein). However, claim 135 is still not enabled because it encompasses fragments as small as 13 amino acids (i.e. SEQ ID NO:43) for which no utility has been demonstrated. Similarly, claim 139 encompasses a protein only 27 amino acids long with no disclosed spreading- or neurite-inhibiting activity. Claim 140 likewise encompasses an unreasonably large number of proteins which do not have the relevant activity.

New claim 138 is similar to previously-presented claim 133, in that it only requires that the protein encoded by the claimed nucleic acid bind to an antibody. There is no requirement that the protein be able to inhibit spreading of NIH3T3 cells, for example. Thus claim 138 reads on an unreasonably large number of possible nucleic acids for which a use has not been

demonstrated. The scope of claim 138 is much broader than that which has been enabled by the specification. Note that in contrast claim 127 complies with the enablement requirement of 35 USC 112, first paragraph as all that is claimed is enabled.

5. Claims 115 – 116, 118 – 119, 123 – 125, 136, 138, and 141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection is maintained for the reasons of record. Briefly, the specification does not provide written description support for claims to:

1) proteins related by sequence identity less than 95% to a disclosed sequence (i.e. claims 115, 118)

2) proteins related by at least 95% sequence identity to a disclosed sequence which do not require inhibition of neurite outgrowth in PC12 cells or spreading in 3T3 cells (i.e. claims 115 – 116, 118 – 119, 136, 138)

3) proteins which induce antibodies or bind to antibodies known to bind to certain regions (i.e. claims 115 – 116, 118 – 119, 138)

Note that for the sake of simplicity claim 138 has been included above, even though it is drawn to nucleic acids, as the nucleic acids encode proteins. The logic set forth here applies to proteins and to the nucleic acids which encode those proteins. If a protein has been sufficiently described, the nucleic acids that encode it are considered described as the genetic code is well-known. However, if a protein is not sufficiently described, the nucleic acids that encode it cannot possibly be sufficiently described.

The examiner notes it would be reasonable to conclude that since more than one protein has been described, each of which has the ability to inhibit spreading in the 3T3 assay or inhibit neurite outgrowth in PC12 cells, it would be reasonable to conclude that the specification describes proteins at least 95% identical to the disclosed sequences, wherein the variant also inhibits spreading in the 3T3 assay or attenuates neurite outgrowth in PC12 cells. However, the specification does not disclose any sequences which are at least 90% identical to the disclosed sequences. While guidance is offered as to how variants might be made, the specification does

not provide evidence that applicant was in possession of the sequence now claimed. The specification does not disclose the structural elements which are common to all claimed variants. The specification does not disclose the structural elements common to all members of the genus of proteins which either bind to certain antibodies or which induce antibodies. These are very broad genera, as the prior art of record (Hopp et al., 1981) teaches that as few as six amino acids are sufficient to elicit an antibody. On page 9 of the Written Description Guidelines, a flow chart is presented which sets forth the criteria to determine if the written description requirement has been met. These include, for example, whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. Here, since any six amino acids can induce an antibody, the claims which recite either antibody binding or ability to elicit an antibody are not considered sufficiently described, because applicant has not shown which structural elements are common to *all members* of the claimed genera.

Note that this rejection could be overcome by limiting the claimed proteins (and nucleic acids encoding them) to proteins at least at least 95% identical to a disclosed protein which inhibit spreading in the 3T3 assay or attenuate neurite outgrowth in PC12 cells, wherein the variant also inhibits spreading in the 3T3 assay or attenuates neurite outgrowth in PC12 cells.

Applicant argues that claims 125 – 132 meet the written description requirement. The examiner concedes that claims 126 – 132 meet the requirement. However, claim 125 depends from rejected claims 115 – 116 and 118 – 119, so claim 125 stands rejected.

6. Claims 136 and 141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

This rejection is maintained for the reasons of record with respect to claim 136. The rejection of claims 117 and 125 – 135 for reciting new matter, set forth in the previous office action, is withdrawn for the following reasons.

Applicant argues, on pp. 27 – 28 of the remarks, that the specification provides sufficient written description for "the carboxy-terminal 188 amino acids of SEQ ID NO:29". Applicant's

arguments are persuasive. Applicant argues that the new matter rejection of claim 117 should be withdrawn because this subject matter is described. However, the subject matter in question has been canceled from claim 117. The subject matter is now recited in claim 140, element (i).

Claim 134 has been canceled; claim 135 has been amended to cancel certain subject matter. Applicant persuasively argues, on p. 29 of the remarks, that support for residues 623 – 640 of SEQ ID NO:2 can be found in the specification as originally filed.

With respect to claim 136, applicant argues, on p. 29 of the remarks filed 4 October 2006, that variants at least 95% identical to the fragments recited in claim 136 are contemplated at p. 15 line 18 – p. 16 line 4 of the specification. This section recites certain short peptide sequences, identified as SEQ ID NO:43 – 46. This section also contemplates variants "substantially similar" to these fragments and defines "substantially similar" to include more than 95% identity. However, the fragments of SEQ ID NO:29 are not recited in this section. SEQ ID NO:30 (which has since be re-defined as SEQ ID NO:29) is listed on p. 15, but the fragments of this sequence do not appear herein. The fragments are listed on p. 17 lines 26 – 27, but the specification does not contemplate proteins "substantially similar" to these fragments. Applicant is improperly mixing and matching divergent concepts set forth in the specification. Therefore the rejection of claim 136 for reciting new matter is maintained, as the originally-filed disclosure did not contemplate variants of these fragments. Claim 141 depends from claim 136 and therefore is rejected as well.

Claim Rejections - 35 USC § 102

7. Claims 127 and 138 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen (1997. Society for Neuroscience Abstracts 23:1723. Abstract presented at 27th Annual Meeting of the Society for Neuroscience, 25 – 30 October 1997).

This rejection is maintained with respect to claim 127 and further extended to claim 138 for the reasons of record and explained in further detail herein. Briefly, Chen (1997) teaches isolation of cDNAs encoding the rat protein bound by antibody IN-1. Chen teaches possession of two rat cDNA sequences, called Oli18 and EST. The declaration filed 4 October 2006 under 37 CFR 1.132 states that the clones reported in the declaration were not full-length, and no sequences were disclosed. However, the reference by Chen (1997) teaches to the public the cDNAs. The cDNAs necessarily will hybridize under the conditions recited in claim 127. The declaration itself provides support for this assertion. At paragraphs (23) – (24), the declaration

discusses how the cDNAs were obtained by screening a cDNA library. Library screening involves hybridization and washing under conditions such as those set forth in the specification, so it is reasonable that the sequences would in fact hybridize. Applicant did not traverse the examiner's reasoning that the sequences now claimed would hybridize under the stated condition. The examiner is unable to determine if the proteins encoded by the cDNAs disclosed to the public in Chen (1997) encode "a protein that displays inhibitory activity in an NIH 3T3 spreading assay" as recited in claim 127. However it is reasonable to presume that the encoded protein will inherently have this property, as the nucleic acids meet the structural limitations set forth in the claim. Claim 138 is rejected as the encoded proteins would be expected to bind to antibodies that also bind SEQ ID NO:2 or 29, since the nucleic acids were isolated in cDNA library-screening procedures using probes designed from proteins that have this property.

On p. 42 – 43 of the remarks, applicant argues that the declaration states that the full-length sequence is not taught in the prior art. Note that claims drawn to proteins comprising full-length SEQ ID NO:2 or 29, or fusion proteins comprising specific amino acids pieced together (for example claim 114), or proteins consisting of specific amino acids, are not subject to this rejection. However, Chen disclosed to the public certain specific cDNA clones. They were available to the public because they were presented at the meeting. Whether or not the sequence was disclosed is not particularly germane. The prior art can be enabling even if the sequence is not disclosed, one can simply obtain the cDNA clone which was disclosed.

Claim Rejections - 35 USC § 103

8. Claims 115 – 116, 118 – 119, 123 – 125, 127, 135 – 138, and 141 rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (1997. Society for Neuroscience Abstracts 23:1723) in view of Sambrook (1989. Molecular Cloning, pp. 16.3 – 16.22 and 17.3 – 17.9) and Bregman et al. (1995. Nature 378:498-501).

The products of claims 115 – 116, 118 – 119, 123 – 125, 135 – 137, and 141 encompass proteins which are at least 90% identical to SEQ ID NO:2 or 29, or proteins comprising fragments of same. The reasons why Chen 1997 anticipates claims 127 and 138 are set forth in the rejection under 35 USC 102(b) above. The examiner is unable to determine which specific amino acids are encoded by the nucleic acids taught in Chen. However, it is reasonable that the encoded proteins are at least 90% identical to SEQ ID NO:2 or 29, and it is

further reasonable that they comprise at least one of the several regions recited in claims 135 – 137, for example. However Chen does not teach methods of making proteins recombinantly.

Sambrook teaches methods of making protein recombinantly, using *E. coli* as the host cell and teaches vectors which are suitable for such purposes (see text excerpted from chapter 17) and also teaches similar methods with eukaryotic cells (see text from chapter 16).

It would have been obvious to one of ordinary skill in the art to insert the nucleic acids of Chen into vectors, put those vectors in host cells, and make protein from the host cells, as taught by Sambrook, with a reasonable expectation of success. A motivation to do so would be to produce large quantities of the protein, which is then useful for making antibodies for therapeutic use, as Bregman teaches such antibodies are suitable for recovery from nerve injury at both the anatomical and functional levels.

On pp. 44 – 45 of the remarks, applicant addressed the examiner's contention that it would have been obvious to follow the protocols set forth in Sambrook. Applicant did not traverse the examiner's assertion that it would be obvious, but rather argued that the starting materials (i.e. the nucleic acids disclosed in Chen) do not contain the full-length nucleic acid. Note that claims drawn to proteins comprising full-length SEQ ID NO:2 or 29, or fusion proteins comprising specific amino acids pieced together (for example claim 114), or proteins consisting of specific amino acids, are not subject to the obviousness rejection.

Priority

9. On p. 30 – 31 of the remarks, applicant argues that all claims are entitled to a filing date of 6 November 1998. Applicant's arguments are persuasive with respect to all claims except claims 136 and 141 (which depends from claim 136). As set forth in the rejection for recitation of new matter, above, support for the variants of fragments recited in claim 136 is not present in the disclosure as originally filed.

Therefore the effective filing date for claims 136 and 141 is 24 September 2001, the filing date of the instant application. The filing date for all other claims under examination (i.e. claims 114 – 119, 123 – 132, 135, 137 – 140 is the date the provisional application was filed, 6 November 1998.

New Rejections

Claim Rejections - 35 USC § 103

10. Claims 114 – 119, 123 – 125, 135, 137, 139, and 141 are rejected under 35 U.S.C. 103(a) as unpatentable over Schwab (U.S. Patent 5,250,414, issued 5 October 1993; cited in IDS filed 19 March 2003), as evidenced by Spillmann et al. (1995. 27th Annual Meeting of the Swiss Societies for Experimental Biology, published in Experientia, Volume 51, p. A44).

These claims encompass the proteins of SEQ ID NO:2 and 29. The specification discloses that SEQ ID NO:2 is rat Nogo-A (see p. 12 lines 13 – 18) and that SEQ ID NO:29 is human Nogo-A, and that these proteins are derived from CNS myelin and inhibit neurite outgrowth. Schwab teaches proteins derived from CNS myelin which inhibit neurite outgrowth. The proteins have molecular weights of 35 and 250 kDa and are bound by antibodies IN-1 and IN-2. See Schwab, column 8, final paragraph, clomun 55, and Table V, for example. The proteins have since be re-named as Nogo; applicant is referred to the office action mailed 6 April 2006, page 14 first complete paragraph for a discussion of the assertion that the 250 kDa protein is in fact "Nogo-A". The examiner notes that applicant did not traverse the examiner's assertion that the 250 kDa proteins described in other prior art references by Dr. Schwab (for example Caroni 1988a and 1988b) are in fact Nogo. Rather, the remarks and declaration presented arguments as to why the prior art references do not anticipate claims to the protein "free of all central nervous system myelin material".

Schwab teaches that myelin derived from several species is suitable as a starting material, and specifically lists human (i.e., relevant to SEQ ID NO:29) and rat (i.e., relevant to SEQ ID NO:2) as species to be used. See Schawb, column 18, line 36 – 40. Schwab teaches the artisan of ordinary skill how to process the tissue to obtain myelin (column 18 lines 36 – 47). Schwab further teaches the artisan how to obtain a protein fraction of 250 kDa from rat tissue; see column 44, line 62 – column 45 line 10 for extraction of myelin, column 45 line 62 – column 46 line 23 for instructions on how to purify the fragments. See also column 48 lines 13 – 24 as to which fragments should be purified.

Schwab teaches that when the 250 kDa band is purified, more than one protein species is present (column 48 lines 23 – 24). The examiner notes that the specific working example of the 250 kDa protein does not anticipate the instant claims, as it is <u>not</u> free of all myelin material. However, Schwab provides detailed guidance as to how to purify the proteins of the invention to homogeneity. See Schwab, '414 patent column 18 lines 51 – 63. Schwab teaches that protein

purification procedures are known in the art, and that they include chromatographic methods and electrophoretic methods such as isoelectric focusing. The reference by Schwab therefore provides not only a motivation to further purify the protein, inherent in the disclosure of multiple products within the single band, but also provides guidance to the artisan as to how to purify the protein. Schwab teaches that the level of skill in the art is high, and that the techniques are well-known in the art.

Furthermore, the reference by Spillmann et al. (1995. 27th Annual Meeting of the Swiss Societies for Experimental Biology, published in Experientia, Volume 51, p. A44) provides evidence that the guidance is in fact sufficient to purify the protein to homogeneity. Spillmann (1995) teaches that "NI-250", a 250 kDa protein derived from bovine myelin which inhibits neurite outgrowth, can be purified by "various chromatography steps". Spillmann teaches that "anion exchange, reverse phase and size exclusion chromatography" can be used to obtain a protein which is 1200-fold more pure than the starting material. Furthermore, the reference by Spillmann provides evidence that this is free of all other myelin material, as it shows "one detectable band at 250 kd in SDS-PAGE" when the gel is silver-stained. Silver is a non-specific protein stain, which can reasonably be expected to identify contaminating proteins bands. Thus the reference by Spillmann provides evidence that the bovine form of the 250 kDa myelin inhibitory protein can be purified by those chromatographic assays described in Schwab ('414 patent). It would therefore be reasonable to expect success in applying these methods to the rat and human proteins disclosed by Schwab.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 114 – 119, 123 – 126, 135, 137, 139 and 141 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2 – 3 of U.S. Patent No. 5,684,133 (cited on IDS filed 19 March 2003). Although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases the claims encompass the proteins now referred to as "Nogo-A". In the '133 patent they are not referred to by this name, but the proteins are disclosed as being 250 kD (note claims 2 – 3 from the '133 patent are generic with respect to molecular weight) and in both cases they have ability to inhibit neurite outgrowth and are bound by antibodies IN-1 and IN-2. Furthermore, the proteins of claims 2 – 3 of the '133 patent are "essentially purified and isolated", which is not patentably distinct from "free of all central nervous system myelin material" as now claimed.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
December 18, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER